Accuracy of Transcranial Ultrasound in the Detection of Mild White Matter Lesions in Newborns

G. CIAMBRA[1], S. ARACHI[2], C. PROTANO[2], R. CELLITTI[2], S. CAOCI[2], C. DI BIASI[3], G. GUALDI[3], M. DE CURTIS[2]

[1] "G. Salesi" Pediatric Hospital; Ancona, Italy
[2] Department of Pediatrics, Umberto I Hospital, "Sapienza" University of Rome; Rome, Italy
[3] Department of Radiology, Umberto I Hospital, "Sapienza" University of Rome; Rome, Italy

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SUMMARY – *Cranial Ultrasound (cUS) may not be sensitive enough to detect subtle white matter (WM) injuries. Our study compared serial cUS with MRI at term equivalent age (TEA) to determine if it is possible to identify an ultrasound representation of subtle diffuse WM injuries such as punctate lesions (PWMLs) and diffuse excessive high signal intensity (DEHSI). Fifty-six very preterm infants were scanned sequentially from birth to TEA, an MRI was performed at TEA. Each echodensity found on cUS was classified as absent, transient (≤7 days), or prolonged (>7 days). A transient periventricular echodensity was detected in seven infants (12.5%), and a prolonged echodensity in 15 (26.8%). MRI examinations were performed in all 56 infants. No altered signal intensity was found in 18 infants (32.1%). DEHSI was detected in 14 infants (25%), and PWMLs were detected in eight babies (14.3%). Both abnormalities were found in 16 infants (28.6%). The positive predictive values of the prolonged echodensity for DEHSI and PWMLs were 86.7% and 46.7% respectively. However, a significant statistical correspondence (p=0.002, Odds Ratio 11.9) was found comparing DEHSI with cUS abnormal echodensities. Serial cUS during the neonatal period in preterm infants is essential and cannot be replaced with MRI at TEA. MRI seems to be more reliable in detecting mild or moderate WM abnormalities. However, serial cUS performed by an experienced neonatologist can provide valuable information on early WM changes such as prolonged echodensities that could potentially lead to a diffuse injury.*

Introduction

Preterm infants are at risk of abnormal neurological development caused by haemorrhagic, ischaemic and inflammatory brain lesions [1]. White matter (WM) injuries could affect a restricted focal area of the brain as in cystic periventricular leukomalacia (cPVL) [2], or they could be diffuse as in punctate white matter lesions (PWML) or diffuse excessive high signal intensity (DEHSI), which may be due to damage or death of the late precursor oligodendrocytes, with secondary impairment of myelination [3,4]. Although cPVL is still the most severe WM injury [3,4], its incidence has decreased dramatically in the last ten years. However, the recent decline of cPVL does not explain the mild cognitive impairments seen in apparently normal infants. It has been suggested that these neurocognitive abnormalities may be due to diffuse non-focal damage to the periventricular white matter [5-7].

Early detection of ongoing brain injury in preterm infants is therefore important to implement or modify preventive treatment. However, few methods that can be used for non-invasive diagnosis and monitoring of brain lesions. Magnetic resonance imaging (MRI) is currently the most accurate method to detect even subtle abnormalities in the brain such as punctate white matter lesions (PWML) or diffuse high signal intensities (DEHSI) [8,9]. MRI, however, is costly,

cannot be used at the bedside, and is impractical for frequent monitoring.

Cranial ultrasound imaging (cUS) is a commonly used technique for the detection and monitoring of major intracranial lesions [1,10]. The method is non-invasive, inexpensive compared to MRI, and relatively widely available, but it is operator-dependent and associated with a high incidence of false positive findings. cUS could potentially be used to observe diffuse WM injury, but there are concerns that the technique may not be sensitive enough to detect subtle abnormalities. Thus, our study aimed to determine the accuracy of cUS in detecting PWMLs and DSHI using MRI as a reference standard.

Materials and Methods

Patients

A total of 56 very preterm infants (gestational age (GA) <30 weeks, and/or birth weight <1500g), admitted to the tertiary neonatal intensive care unit of Rome, Sapienza University between December 2010 and March 2012 were eligible for a retrospective neuroimaging study. Inclusion criteria were a complete series of cUS exams and MRI at TEA. Exclusion criteria were an incomplete series of cUS examinations or a missing MRI at TEA, congenital anomalies and chromosomal disorders. Eligible infants received serial cUS examinations and an MRI at term of gestational age according to our standardized protocol for premature infants.

Cranial Ultrasound

Sequential cranial ultrasound scans were obtained using a standardized protocol with images acquired within 24 hours after birth, then at 72 hours, at seven to ten days, weekly until discharge and again on the day of the MRI examination around TEA. If any abnormality was detected or in case of clinical issues, further cUS assessments were undertaken. All the images were acquired with 5-9 MHz convex probes by using a Voluson 730 Expert GE system. A standardized series of images were obtained at every examination [1]. Six coronal views (at the level of the orbits, middle cerebral arteries, third ventricle, fourth ventricle, bodies of lateral ventricles and centrum semiovale) and five sagittal-parasagittal views (midline, ventricles, periventricular white matter) were obtained through the anterior fontanelle. Two experienced neonatologists, blind to the MRI imaging results, analyzed all cranial ultrasound scans.

Although the cUS scans were analyzed extensively, for the purpose of this study we focused on WM echodensities. Abnormal periventricular echodensity was defined as an increased intensity in the periventricular WM which appeared equal to or higher than the choroid plexus's intensity. Peritrigonal flush was excluded.

Each echodensity found was classified as absent, transient (≤7 days of duration), or prolonged (>7 days of duration). The investigators were blinded to the MRI imaging findings.

MRI Imaging

MRI examinations were performed according to the study protocol around TEA.

MRI imaging was performed with a 1.5 Tesla Philips Gyroscan. Scans included at least T1-weighted three-dimensional images (TR/TE = 20 ms/6.9 ms, slice thickness 1mm), T2-weighted TSE images (TR 4600 ms, TW 1000 ms, slice thickness 4-5 mm) and diffusion-weighted images DWI.SSH [4,9].

An experienced neuroradiologist, blind to the US data, then proceeded to evaluate the MR images. Although the MR images were analyzed extensively, for the purposes of the study, we focused on the presence and severity of WM signal intensity abnormalities such as PWML and DEHSI.

PWML were defined as small areas of high signal on T1-weighted images with mostly low signal on T2-weighted images. DEHSI was defined as areas of excessive high signal intensity diffusely distributed within the periventricular and/or subcortical WM on T2-weighted images [11,12].

Data Analysis

Statistical analyses were performed using PASW statistics version 17.

The value of cUS at predicting WM abnormalities, as shown on MRI images at term, was assessed by calculating the sensitivity, specificity, positive and negative predictive value, and odds ratio. c-US findings and MRI findings were correlated by calculating Pearson's coefficient which was considered significant when <0.05.

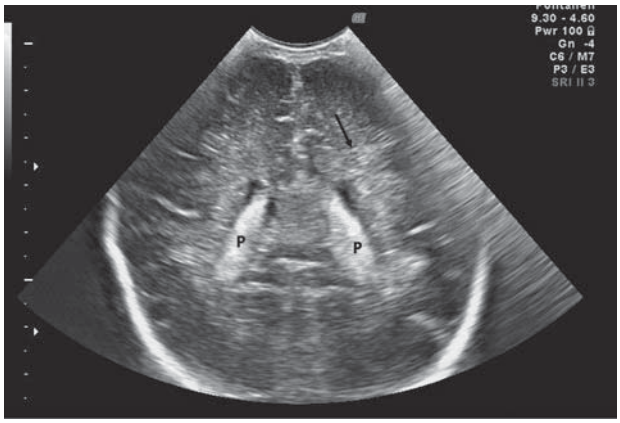

Figure 1 Posterior coronal view of a prolonged periventricular echodensity in a preterm infant born at 28 weeks gestation, cranial ultrasound performed at 21 days of life. (P: choroid plexus; arrow: periventricular echodensity).

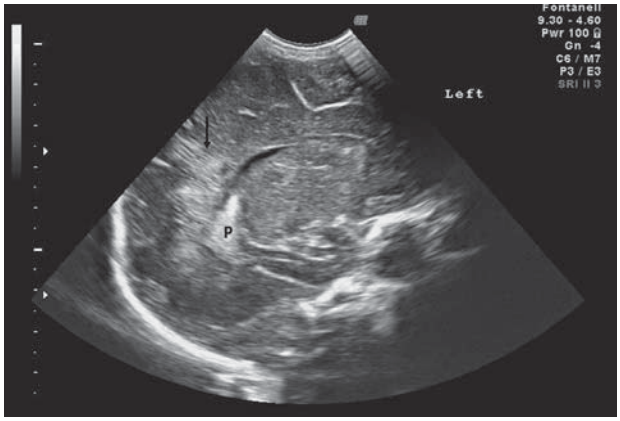

Figure 2 Sagittal view of a prolonged periventricular echodensity in a preterm infant born at 28 weeks gestation, cranial ultrasound performed at 21 days of life. (P: choroid plexus; arrow: periventricular echodensity).

Results

Cranial Ultrasound

Fifty-six preterm infants (27 male and 29 female) were studied, mean gestational age was 27.98 ± 1.96 (24-30 weeks GA) and mean birth weight was 1095.27 ± 292.66 g. Informed parental consent was obtained for all of them. No abnormal periventricular echodensity was found in 34 of the 56 babies (60.7%). A transient periventricular echodensity (≤7 days of duration) was detected in seven infants (12.5%), and a prolonged echodensity (>7 days of duration) in 15 (26.8%) (Table 1, 2) (Figures 1 and 2).

MRI Imaging

MRI examinations were performed in all 56 infants around TEA (range 39-41 weeks of postmenstrual age). Informed parental consent was obtained for all of them. No altered signal intensity of the WM was seen in 18 infants (32.1%). An abnormal pattern of the WM signal intensity was shown in 38 babies (67.9%). An excessive high signal intensity diffusely distributed within the periventricular and/or subcortical WM (DEHSI) was detected in 14 infants (25%) (Figure 3) (Table 1), and small areas of high signal on T1-weighted images (PWMLs) were detected in eight babies (14.3%) (Figure 4). Both abnormalities were found in 16 infants (28.6%). PWMLs were seen in 24 babies (42.9%), nine of which (16.1%) as a single lesion, 15 (26.8%) as multiple areas as seen in Table 2.

Table 1 Comparison between cranial ultrasound (cUS) findings and the appearance of diffuse excessive high signal intensity (DEHSI).

cUS findings	**MRI DEHSI**	
	Absent (n=26)	DEHSI (n=30)
Normal (n=34)	22	12
Transient (n=7)	2	5
Prolonged (n=15)	2	13

p-Value: 0.002

Table 2 Comparison between cranial ultrasound (cUS) findings and the appearance of punctate white matter lesions (PWML).

cUS findings	**MRI PWML**		
	Absent (n=32)	PWML single (n=9)	PWML multiple (n=15)
Normal (n=34)	20	7	7
Transient (n=7)	4	1	2
Prolonged (n=15)	8	1	6

p-Value: 0.592

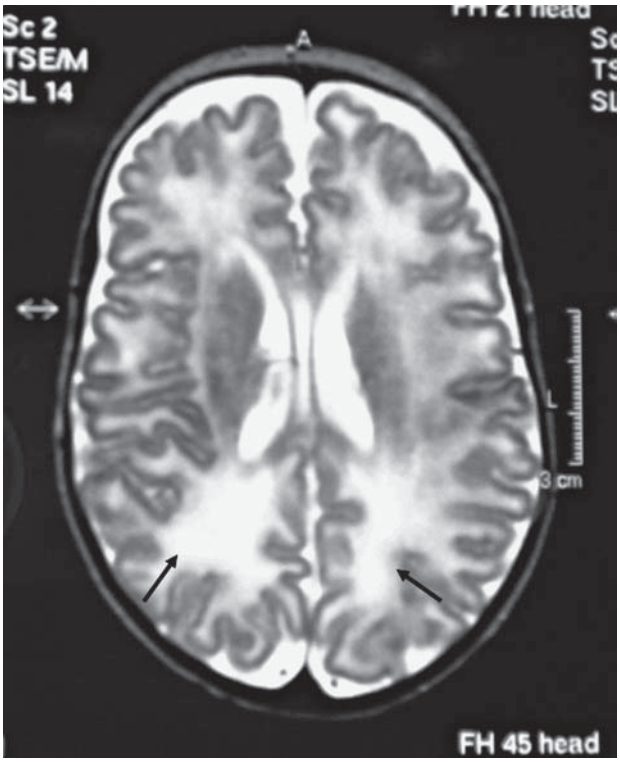

Figure 3 T2-weighted MRI at term equivalent age, axial plane of a preterm infant born at 28 weeks showing (arrows) diffuse high signal intensity (DEHSI) within the periventricular white matter.

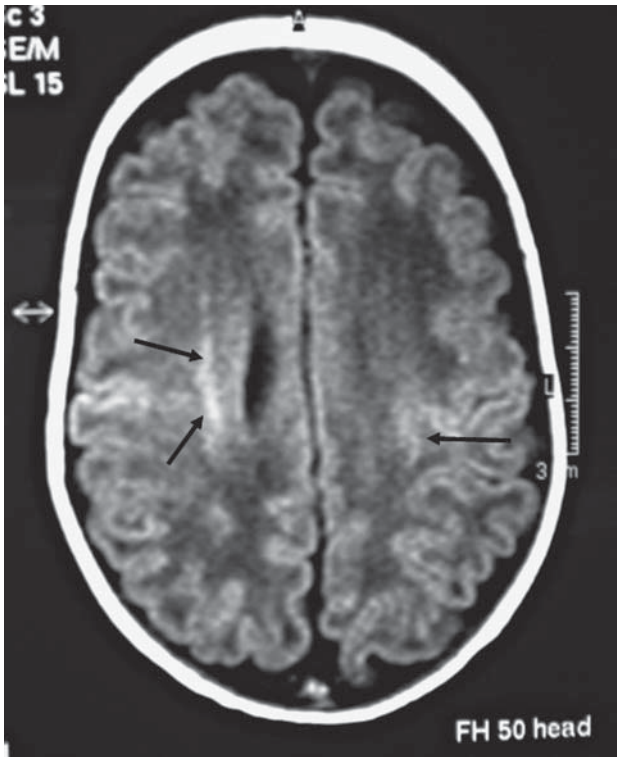

Figure 4 T1-weighted MRI at term equivalent age, axial plane of a preterm infant born at 27 weeks showing multiple small punctate lesions (arrows) beside the corona radiata.

Discussion

This study presents population-based data on the comparison between serial cranial ultrasound (cUS) findings and conventional MRI performed at term equivalent age in a cohort of preterm infants for the detection of subtle white matter (WM) abnormalities.

We found that the accuracy of cUS in predicting WM lesions as measured using sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) was relatively high. However, sensitivity was found to be low for the detection of punctate white matter lesions (PWML). The same result, even if less strong, came out analysing the sensitivity of cUS in detection of DEHSI. When using US for the detection of subtle and diffuse WM lesions, a high specificity with a low sensitivity of the test could reasonably be a technique-based bias due to the low resolution of ultrasound; the limitation of US scans could, however, be reduced using good equipment in experienced hands.

No significant statistical correspondence was found between ultrasound images of normal or abnormal periventricular echogenicity and punctate lesions (p=0.592). On the other hand, the most interesting result emerges comparing DEHSI with ultrasound-prolonged echodensities. We found a significant statistical correspondence between the appearance of the two patterns (p=0.002), and comparing the variables the Odds Ratio was 11.9, meaning that every infant with a prolonged echodensity has an 11.9 times higher probability of developing a DEHSI. This result, proven on a larger population, could give prolonged echodensities a predictive value for diffuse white matter injury and therefore cUS would have a more important role in predicting WM subtle abnormalities.

Leijser et al. [13] found that all bilateral symmetrical echogenic areas in the frontal and periventricular WM seen in early preterm US scans correlate well with areas of altered signal intensity in WM on MRI.

In 2010 Horsch et al. [14] demonstrated that all severe WM abnormalities detected by MRI at TEA were also identified on cUS performed on the same day. Infants with normal cUS at term

Table 3 Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of cranial ultrasound (cUS) abnormalities for punctate white matter lesions (PWML).

cUS findings	**Measures of cUS accuracy - PWML**			
	Sensitivity	Specificity	PPV	NPV
Total abnormalities	41.7%	62.5%	45.4%	58.8%
Transient	17.6%	83.3%	42.9%	58.8%
Prolonged	33.3%	71.4%	46.7%	58.8%

Table 4 Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of cranial ultrasound (cUS) abnormalities for diffuse excessive high signal intensity (DEHSI).

cUS findings	**Measures of cUS accuracy - DEHSI**			
	Sensitivity	Specificity	PPV	NPV
Total abnormalities	60%	84.6%	81.8%	64.7%
Transient	29.4%	91.7%	71.4%	64.7%
Prolonged	52%	91.7%	86.7%	64.7%

age were instead found to have normal or mild WM abnormalities on MRI.

Although for the purpose of this study we focused only on subtle WM abnormalities, we share the same result that all the severe features typical of prematurity such as intraventricular haemorrhage or cPVL detected by MRI had been previously shown by ultrasound scans.

In another study Leijser et al.[15] tried to correlate sequential cUS from birth to TEA with MRI performed at term, finding that ultrasound is less reliable for mildly and moderately abnormal WM injuries.

One limitation of this study is that data on long-term neurodevelopmental outcome are not yet available, and consequently the clinical impact of our findings cannot be evaluated. Clinical follow-up of all enrolled infants is currently ongoing. Finally, for this study the anterior fontanelle was the only acoustic window used through which the occipital region is not optimally visualized.

In conclusion, our results agree with other literature studies showing that cranial ultrasound is less precise to estimate subtle WM injuries in preterm infants, and that an ultrasound representation of PWMLs and DESHI has not yet been found. However ultrasound, performed sequentially from birth to TEA by an experienced neonatologist, can provide valuable information on early WM changes that, as demonstrated, could potentially lead to diffuse injuries. Further studies are required to establish if findings such as transient or prolonged echodensities could be considered a risk factor for developing diffuse WM injury in preterm infants.

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Dr Stefano Caoci
Department of Pediatrics
"Sapienza" University of Rome
Viale Regina Elena 324
00161 Rome, Italy
E-mail: stefanocaoci@gmail.com